DRUG INFORMATION ASSOCIATION

42nd Annual Meeting

Prescription Drug Labeling:
Implementation of FDA's New Regulation for the Content and Format of the USPI and Accompanying Documents

June 19, 2006

Philadelphia 2006

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Introduction to the New Content and Format of Labeling: "Physician's Labeling Rule (PLR)"

Steven W. Bass, PhD
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Learning objectives

At the conclusion of this session, participants should be able to:

- Gain familiarity with the Physician's Labeling Rule (PLR) and accompanying guidance documents
- Understand the major changes and improvements to the USPI and general principles for converting to new format
- Identify products affected by the PLR and corresponding implementation schedules
- Understand how PLR in SPL format will facilitate various e-labeling initiatives
- Gain insight into FDA's interpretation of the new regulations and guidance documents through the Q & A

Session Overview

- **Regulatory History**
- **PLR Overview**
- **Q and A**
  - **DIA Labeling SIAC Discussions**
  - **DIA Webinar (March 21)**
  - **FDA/DIA Hands-on Workshop (May 4-5)**
  - **CDER Live (May 9)**
- **Audience Questions**

Regulatory History

- **The Current Rule:**
  - 44 FR 37462, **June 26, 1979** (201.56, 201.57, 201,100)
    - **FR Dec. 13, 1994 – Pediatric Final Rule - Effective December 13, 1996**
    - **FR Aug. 27, 1997 – Geriatric Final Rule - Implement based on NDA app. Date - by 8/27/2003 all labeling must have Geriatric Section**
    - **CFR 201.24 – Final Rule: FR Feb 6, 2003 – Effective Feb 6, 2004: Labeling Requirements for Systemic Antibiotic Drug**
  - **FDA Sponsored Public Meeting – October 30, 1995**
  - **FR December 22, 2000 – Proposed Rule**
  - **FR January 24, 2006 – Final Rule**

PLR - fully integrated with the Guidance Documents

Final Rule on Requirements for Prescribing Information

1/24/2006

Still to come:

Clinical Pharmacology Section

Dosage and Administration Section

Implementing the New Content and Format Requirements

Draft Guidance

Warnings & Precautions, Contraindications, and Boxed Warning Sections

Draft Guidance

Adverse Reactions Section

Final Guidance

Clinical Studies Section

Final Guidance

4 Fictitious examples

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Implementation of FDA's New Regulation for the Content and Format of the USPI and Accompanying Documents

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Agenda

- PLR Overview
- PLR process issues
- Integration of PLR with SPL
- Q and A

21 CFR Sections

§ 201.56	General labeling requirements
§ 201.57	Specific requirements for "newer" drugs (HL, Contents, FPI)
§ 201.58	Waiver provision
§ 201.80	Specific requirements for "older" drugs (formerly § 201.57)
314.70	Supplements and other changes to an approved application

Goals for new labeling rule

- More informative labeling
- More accessible labeling
- More memorable labeling
- Better risk communication
- Fewer medication errors

Overview of format changes to labeling

- **Highlights**
  - High level summary (half page max)
  - Links to appropriate section of Full Prescribing Information (FPI)
- **Contents (table of)**
  - Consistent order and numbering of sections
  - Links to FPI
- **FPI**
  - Frequently referenced info moved forward (except for Patient Counseling Info, now required and appears last)
  - Safety info consolidated (Warnings and Precautions)

New Sections of Labeling

- **Formerly in *Precautions***
  - ***Drug Interactions***
  - ***Use in Specific Populations***
  - ***Patient Counseling Information***
- **Formerly optional**
  - ***Clinical Studies***
  - ***Nonclinical Toxicology***
- **Formerly in *How Supplied***
  - ***Dosage Forms and Strengths***

Established Pharmacologic Class

- ***Highlights Indications*** **section:**
  - **"This drug is a _____ indicated for…."**
- **Important for prescribing decisions (e.g., avoid drug interactions)**
- **Pharmacologic class may be defined by 1 or more types of terms**
  - **Mechanism of action**
  - **Physiologic effect**
  - **Structural class**
- **If not "established," exclude the term**
- **Guidance under development**
- **Pharmacology Class Coordinating Committee also under development**

Revisions to Safety Requirements

- ***Boxed Warning***
  - Appears in *Highlights* in bulleted format, limited to 20 lines
  - Repeated in full text at beginning of *FPI*
- ***Contraindications***
  - Include only known hazards
  - Only list patient groups where risk clearly outweighs any possible benefit
- ***Warnings and Precautions***
  - Expanded to include clinically significant adverse reactions
- ***Adverse Reactions***
  - Include only reactions with some basis for causal relationship to drug
  - Separate listings of ARs from clinical trials and ARs from spontaneous reports
  - Pool AR profile using data from all trials

Other New Requirements

- **Dosing regimens and indications/uses implied in any other sections must be listed in D&A and I&U.**
- **I&U includes limitations of use and conditions of use**
  - Uncertainty about anticipated benefit (e.g., approval based on a surrogate)
  - Approved as adjunct treatment only
  - Limited info in an important patient group
- **Explicit requirement to update labeling when new information becomes available**

Recent Major Changes

- **Identified and dated in HL**
- **Margin mark in FPI**
- **Required for changes to:**
  - Boxed Warning
  - Indications and Usage
  - Dosage and Administration
  - Contraindications
  - Warnings and Precautions
- **Remain for 1 year**

Other improvements

- **Emphasizes "Patient Counseling Information"**
- **Encourages AR reporting**
  - FDA contact information (phone and internet address) for reporting AEs
  - Industry phone/internet address if dedicated to AE reporting
- **Adds initial US approval date**
- **Adds date of labeling revision**

Example of Contents for a Fictitious Drug

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

Example of Highlights for a Fictitious Drug

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

***See full prescribing information for complete boxed warning*.**

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

----------INDICATIONS AND USAGE----------

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

Affected Products

- **New NDAs, BLAs and efficacy supplements**
- **Applications approved up to 5 years prior to 6/30/06**
- **Encouraged voluntary compliance by older products**
- **ALL products must append ALL FDA-approved patient labeling by June 30, 2007**
  - Applies to “older” products
  - Can be submitted in the Annual Report

Implementation Schedule

New NDA/BLA or efficacy supplement submitted:	Label must conform:
6/30/06 or after	At time of submission
Pending on 6/30/06 Approved 6/30/05-6/30/06	6/30/09 (3 years)
Approved 6/30/04-6/29/05	6/30/10 (4 years)
Approved 6/30/03-6/29/04	6/30/11 (5 years)
Approved 6/30/02-6/29/03	6/30/12 (6 years)
Approved 6/30/01-6/29/02	6/30/13 (7 years)
Approved Pre-6/30/01	Voluntary at any time (encouraged to conform)

Prior-approval labeling supplements required

- **For revision to new requirements adding *Highlights***
- **For future changes to *Highlights***
  - Exceptions that may be submitted with Annual Report:
    - *Removal of a listed section from "Recent Major Changes" after 1 year*
    - *Changes to the revision date*

Waivers

- **Expanded over previous requirements**
- **May be requested to waive any requirement under 201.56, 201.57, or 201.80.**

General Principles for Converting Labeling

- **No additional data analyses unless recent information causes labeling to be inaccurate**
- **Unique opportunity to evaluate and update claims in labeling**
- **Unless inapplicable, missing sections must be developed**
- **Labeling info may**
  - Transfer in its entirety to a new section
  - Be divided between sections
  - Be repeated in different sections in varying levels of detail, avoiding redundancy
- **Combine and consolidate info about similar issues under one subheading, if possible**
- **Use cross-referencing**

Electronic Labeling Initiatives

- **Structured Product Labeling (SPL) is the content of labeling in a standardized electronic file format with tagged blocks of text and coded data elements**
  - Use of this common format will enable all parties to create, send, and receive product labeling content
  - Coded data elements will enable Decision Support Systems to develop query functions
- **PLR facilitates eLabeling initiatives**
  - eHealth records
  - ePrescribing
  - Daily Med
    - Electronic repository populated by current FDA labeling managed by NLM

SPL PLR format submissions

- **SPL PLR implementation guide available in draft**
- **Additional data element requirements**
  - Highlights data elements
  - Data Council website provides “stylesheet” for PLR data elements
  - Additional guidance pending